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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
GIUSEPPE ARPAIA, ET AL.	: EXAMINER: XU, X.
SERIAL NO: 10/556,803	:
FILED: NOVEMBER 14, 2005	: GROUP ART UNIT: 1797
FOR: METHOD OF CHROMATOGRAPHIC ANALYSIS OF A PROTEIN SOLUTION	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

In accordance with 35 U.S.C. § 134, that the claims of the present application have been twice rejected, this brief is submitted in response to the final rejection dated February 3, 2010.

REAL PARTY OF INTEREST

The real party of interest is Ares Trading, S.A., Aubonne, Switzerland.

RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 15-17 are active.

Claims 15-17 are rejected.

Claims 15-17 are appealed.

Claims 1-14 and 18-24 were cancelled.

The appealed claims are presented in Appendix I.

STATUS OF AMENDMENTS

No outstanding amendments are present in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the pending, rejected and appealed independent claim 15 with reference to exemplary support in the originally filed application is:

A method of chromatographic analysis of follicle stimulating hormone (FSH) protein in a sample for quantifying the total FSH protein wherein the method comprises: **[page 1, lines 15-18, page 4, lines 10-18, and page 11, line 15]**

preparing the protein sample by adding 100 μg[1]/ml of poloxamer 188 (Pluronic F68) in ultra pure water to the sample; **[page 6, lines 10-12; and page 11, lines 19-20]**

performing chromatography on the protein sample; and **[page 3, lines 19-23, page 4, lines 10-18, page 11, lines 19-20]**

manipulating data to determine the quantity of the total FSH protein, wherein the quantity of the total FSH protein is determined using data from calibration with a standard. **[page 4, lines 19-21]**

[1] There is a typographical error in Claim 15 as "g" is noted but as outlined in the Action at page 2, μg is intended. Applicants will correct this after a decision has been reached on the merits of the obviousness rejection appealed herein.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole ground of rejection to be reviewed on appeal is whether Claims 15-17 would have been obvious under 35 USC 103(a) in view of Katakam *et al* (*Pharmaceutical development and Technology*, 1997) in view of Wu (*Journal of Endocrinology, 1993*).

ARGUMENT

I. The invention

The claims of this application are directed to a method for the chromatographic and quantitative analysis of proteins in which a poloxamer surfactant is added to the protein solution. That method as defined in Claim 15 includes three steps:

1. preparing the protein sample by adding 100 μg/ml of poloxamer 188 (Pluronic F68) in ultra pure water to the sample;
2. performing chromatography on the protein sample; and
3. manipulating data to determine the quantity of the total FSH protein, wherein the quantity of the total FSH protein is determined using data from calibration with a standard

As discussed in the specification on pages 3 and 4 the addition of the poloxamer surfactant in the manner and concentration as defined in the claims avoids protein loss and does not interfere with analysis in determining purity and concentration. The examples of this application provide a number of statistical analyses demonstrating that the addition of the specific poloxamer in the manner and concentration as defined in the claims to an FSH sample provide this effect, see Table 10 at page 32 of the specification.

II. The rejection

The Examiner finds that Katakam teaches the use of Poloxamer 188 to a sample, performing chromatography, and determining the quantity of total protein by UV absorbance (see page 2, last paragraph of the final Official Action).

The Examiner finds that Katakam teaches a range of Poloxamer from 0.001% (below cmc) to 0.2% (above cmc) citing Table 1 and that 100 μ/ml is equivalent to 0.01% (see page 3, 1st paragraph of the final Official Action).

The Examiner finds that even though Katakam does not teach a calibration curve, such is well known and therefore obvious (see page 3, 2nd paragraph of the final Official Action).

The Examiner concedes that Katakam does not teach FSH, the subject matter defined in the claims and thus reaches into Wu, who teaches FSH isolation by chromatography (see page 3, 4th paragraph of the final Official Action).

Based on these findings, the Examiner concludes that "it would have been obvious for one of the ordinary skill in the art to apply the same method on other proteins. From particular to general is how science and engineering developed." (See page 3, 5th paragraph of the Official Action).

III. The claims would not have been obvious in view of Katakam and Wu

The significance of the Examiner's conclusion can be understood only when it is considered in light of the wealth of clearly erroneous findings which immediately precede it. Conclusions of obviousness based on clearly erroneous findings, as is here the case, cannot stand. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006).

First, Katakam does not describe FSH only HGH (human growth hormone) and while this fact is acknowledged in the rejection, the true nature of the differences between these proteins and the failure of the underlying combination of prior art to even know how to address problems with FSH in chromatograph or even that a problem may have existed with FSH. Indeed, there are no teachings in Katakam that allow one to envision the effects of Poloxamer surfactants on FSH. While it is true that Wu describes isolating FSH from bovine pituitary glands and Katakam discusses effects of HGH aggregation in the presence of poloxamer, there are no teachings in this combination of art that even remotely suggests any problems with FSH.

HGH and FSH are very different proteins, have remarkably different structures and how one protein (HGH) acts in a given set of experiments (like in Katakam) provides no reasonable guidance as to how a second, distinct protein (FSH from Wu) would behave.

HGH is a protein of about 200 amino acids and a molecular weight of 22 KD. The structure includes four helices for functional interaction with its receptor. The three-dimensional structure of HGH reported at RCSB Protein Databank (http://www.rcsb.org/pdb/home/home.do) is:

In contrast, FSH is a **glycoprotein** composed of ***two*** polypeptide monomers, α and β. The three-dimensional structure of FSH reported at RCSB Protein Databank (http://www.rcsb.org/pdb/home/home.do) is:

The combination of Katakam and Wu do not provide any teachings as to how to assess total FSH protein in a chromatographic method as is defined in the claims.

Persons having ordinary skill in the art normally seek "to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). However, before persons having ordinary skill in the art would want to optimize the choice or use of components in a claimed process, the prior art must at least generally recognize the process and generally suggest the components the claimed process utilizes to achieve its goals. To establish that Applicants' claimed process would have been obvious to a person having ordinary skill in the art, the prior art must reasonably suggest that persons having ordinary skill in the art do what Applicants claims require. Here, the only suggestion to do what Applicants have done is Applicants' own disclosure, i.e. hindsight.

Where, as here, the rejection of the subject matter Applicants claim is based on hindsight, the rejection is improper. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). *In re Fritch*, 972 F.2d at 1266; *In re Fine*, 837 F.2d at 1075.

Further, consider the Examiner's conclusion of obviousness at page 4, 5th paragraph that "it would have been obvious to one of ordinary skill in the art to apply the same method on other proteins." This conclusion has failed to address or even acknowledge that while it may be obvious to try, there must be a reasonable expectation of success and the dramatic differences in the two proteins at issue here cannot be reasonably expected to behave in similar manners. Anyone who has ever performed protein purifications would know this as true.

Indeed, the fundamental reasoning underlying the rejection is flawed and erroneous. The Examiner concludes that the it would have been obvious to use any Poloxamer based on Katakam's teachings, however, the Examiner ignores the fact that following the teachings of Katakam, one would not have used Poloxamer 188 for size exclusion chromatography as alleged in the rejection. Table 1 (page 147) in Katakam clearly shows that Poloxamer 188

was the worst stabilizer amongst those tested. In fact, looking at the column corresponding to the critical micelle concentration (cmc) of each surfactant, it results that by using Poloxamer 188, a high level of protein aggregates were obtained (0.66) with very low soluble protein (0.03 mg/ml), which was the lowest of those surfactants tested.

More specifically, according to Katakam et al. (see Table 1, page 147) the **cmc** of Poloxamer 188 is 0.0055 g/dl, which is equal to 0.0055 g/100 ml.

The concentration of a solution is often expressed as a "weight/volume percentage"; the percentage is calculated from the weight of solute in grams (g), divided by the volume of solvent in milliliters (ml): [Mass(g) / Volume(ml)] × 100 = %. In this case: (0.0055 g/100 ml) × 100 = **0.0055%**, which is the cmc of Poloxamer 188 according to Katakam et al.

Based on this and looking at the results reported on Table 1, it possible to conclude that Poloxamer 188, amongst those tested, is the worst stabilizer at a concentration between 0.001% (below cmc) and 0.0055% (at cmc). According to Table 1, Poloxamer 188 becomes a good stabilizer at a concentration of 0.2%, which is over 36 times of the cmc of Poloxamer 188 according to Katakam et al.

To compare the concentrations of Poloxamer 188 tested in Katakam et al. with that recited in Claim 15 (100 μg/ml) a calculation of concentrations to the same units is provided below:

100 μg/ml = 10000 μg/100 ml = 0.01 g/100 ml which, applying the formula above, corresponds to **0.01%**, i.e. a little less than double the cmc of Poloxamer 188 according to Katakam et al. (0.01/0.0055=1.81).

Therefore, it follows that the concentration of Poloxamer 188 recited in Claim 15 (0.01%) is much closer to the "non-working" concentration of Poloxamer 188 (0.0055%), according to Katakam et al., than to the "working" concentration (0.2%).

Therefore, contrary to the underpinnings of the rejection, the skilled person would have had no motivation to try Poloxamer 188 as stabilizer at a concentration which is less than double the cmc, knowing that Poloxamer 188 works well at much higher concentrations, i.e. concentrations over 36 times the cmc.

The fact that Poloxamer 188 is a good stabilizer for FSH at a certain concentration, which is very close to that which showed very negative results for hGH, is evidence that these two proteins have totally different properties. Therefore, one would not have not been motivated to apply the teaching of Katakam, focused on hGH, to FSH as in Wu and the present claims and would one be so motivated, a reasonable expectation of success would not be the logical result.

The Examiner again raises an argument that is based on an erroneous reading of the cited prior art and specifically in the final Official Action at page 4, the Examiner referred to the discussion on page 146, left column of Katakam to allege that generally "cmc is a critical concentration that needs to be exceeded in order to form a complete monolayer at the surface of the micelle."

While the amount of poloxamer in the claims is twice the cmc reported in Katakam, the Examiner's conclusion that generally Katakam teaches that all poloxamers are required to be at least twice the cmc is incorrect. Specifically in the same section on page 146, left column of Katakam, the Examiner has failed to appreciate Katakam clearly states **below and at** the cmc, poloxamer 407 was found to be effective. Therefore, contrary to supporting the Examiner's position the actual teachings of Katakam taken in its entirety do not support that twice the cmc is required providing further evidence, from the very prior art cited in the rejection, that while something may be obvious to try, there would not have been a reasonable expectation of success. See also, *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd,* 533 F.3d 1353, 87 U.S.P.Q.2D 1452 (Fed. Cir. 2008): "To the extent an art is unpredictable, as the

chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

IV. Conclusion

For the reasons stated in this Brief, Appellants respectfully request that the Examiner's rejections be withdrawn with direction to allow all of the claims pending in this application and pass this case to issue.

Respectfully submitted,

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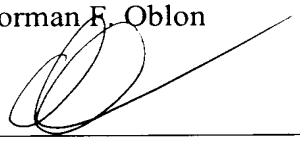
Norman F. Oblon



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APPENDIX 1 (CLAIMS)

Claim 15 (Rejected): A method of chromatographic analysis of follicle stimulating hormone (FSH) protein in a sample for quantifying the total FSH protein wherein the method comprises:

preparing the protein sample by adding 100 g/ml of poloxamer 188 (Pluronic F68) in ultra pure water to the sample;

performing chromatography on the protein sample; and

manipulating data to determine the quantity of the total FSH protein, wherein the quantity of the total FSH protein is determined using data from calibration with a standard.

Claim 16 (Rejected): The method of claim 15, further comprising diluting the protein sample prior to performing chromatography.

Claim 17 (Rejected): The method of claim 15, wherein the chromatography is size-exclusion chromatography (SEC) or reverse phase HPLC (RP-HPLC).

APPENDIX II (EVIDENCE)

1. The present specification, referenced in the arguments presented in this brief.
2. The three-dimensional structure of HGH reported at RCSB Protein Databank (http://www.rcsb.org/pdb/home/home.do) submitted and entered into the record on April 24, 2009.
3. The three-dimensional structure of FSH reported at RCSB Protein Databank (http://www.rcsb.org/pdb/home/home.do) submitted and entered into the record on April 24, 2009.

APPENDIX III (RELATED APPEALS AND INTERFERENCES)

None.